

Robust Stability of Genetic Regulatory Networks with Stochastic Time Delays Under Intrinsic and Extrinsic Noises

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Abstract—Gene regulation is inherently a stochastic process due to intrinsic and extrinsic noises which cause the fluctuations and uncertainties of kinetic parameters. On the other hand, time delays are usually inevitable due to different biochemical reactions in the genetic regulatory networks (GRNs) which are also affected by noises. Therefore, in this paper, we propose a GRN model that is subject to additive and multiplicative noises as well as random time delays. Robust stochastic stability of such GRNs with disturbance attenuation is analyzed by applying the control theory and mathematical tools. Based on the Lyapunov method, new stability conditions are derived in the form of linear matrix inequalities (LMIs) that are dependent on the statistical properties of stochastic time-delays. An example is employed to illustrate the applicability and usefulness of the developed theoretical results.

I. INTRODUCTION

Gene expression, as defined by the set of reactions that control the abundance of gene products, influences most aspects of cellular behavior, and its variation is often invoked to explain phenotypic differences in a population of cells. Because DNA, RNA and proteins can be present and active at a few copies per cell, the abundance of gene products is theoretically sensitive to stochastic fluctuations. We use the term “noise” in gene expression to refer to the measured level of variation in gene expression among cells, regardless of source, within a supposedly identical population [18].

Since molecular events in cells are subject to significant thermal fluctuations and noisy process with transcriptional control, alternative splicing, translation, diffusion and chemical modification reaction, the gene expression is best viewed as a stochastic process. Many observations suggest that molecular events underlying cellular physiology experience fluctuations, which gives rise to the proposal of stochastic models for gene expressions and biofunctions [12], [13], [22], [23].

A stochastic differential equation or the Langevin equation has been employed to describe the molecular fluctuation in

gene networks [7], [12]. Many algorithms have been developed for simulating the Langevin equation to calculate the probability density function [5], [14], [16], [22]. The Fokker–Plank equation has been employed to describe the evolution of the probability function [9], [20]. Most researchers have analyzed these stochastic models, using the Monte Carlo method such as Gillespie algorithm [6], etc., to describe the evolution of biochemical networks via the discrete stochastic model.

The noise sources could generally be partitioned into two categories: intrinsic noise and extrinsic noises [21]. Intrinsic noise is determined by the structure, reaction rates, and species concentrations of the underlying biochemical networks [22]. Differences between cells, either in local environment or in the concentration or activity of any factor that affects gene expression, will result in extrinsic noise. On the other hand, parameters of the model are fluctuating owing to the noise from different sources. Therefore, a key starting point in developing a conceptual and theoretical bridge to biology is the robustness, the preservation of particular characteristics despite uncertainty in components or the environment [3].

Biochemical process delays could lead to fluctuation, oscillation or even blowing up for an engineered biochemical network [1]. Subsequently, biochemical process delays should be taken into account in the dynamic model to mimic the realistic cellular behaviors of biochemical gene network in cell. Usually, time delays in GRN model are assumed to be constant but, due to the stochasticity of GRN, we can hardly obtain the exact values of the time-delay. In real-time experiments, we may only be able to have some statistical property of time delays, e.g., mean and variance values. In this case, we can model stochastic time delays as $\tau(t) = \tau_0 + \xi_\tau(t)$, where $\xi_\tau(t)$ is a white noise term. Different from the traditional time-varying delays which have been investigated extensively, for which the time-varying delay is assumed to be differentiable, the stochastic time-delay considered here is time-varying but no longer differentiable. The introduction of such kind of stochastic time-delays is not only for a better approximation of GRNs, but also for bringing a potential research topic to the control society.

This paper presents robust stability conditions for GRN with stochastic time delays. Intrinsic and extrinsic noises from different sources are considered in modeling GRN. Noises are also utilized to characterize the GRN model uncertainties. These conditions are formulated in terms of linear matrix inequalities, which can be readily solved by using standard numerical software. By utilizing some advanced

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techniques, both the expected value and finite variance of stochastic delays are brought into the final robust stability conditions. A GRN example illustrates the applicability and usefulness of the developed theoretical results.

II. PROBLEM FORMULATION AND PRELIMINARIES

The activity of a gene is regulated by other genes through the interactions between them, i.e., the transcription and translation factors. Here, the regulation can be regarded as the feedback, i.e., the level of gene expressions as a function of the concentration of transcription factors. Taking the time delay into account, the following delayed GRN model is proposed in [11], [19]:

$$\begin{aligned}\frac{dm_i(t)}{dt} &= -e_i m_i(t) + \sum_j G_{ij} g_j(p_j(t - \tau)) + l_i, \\ \frac{dp_i(t)}{dt} &= -c_i p_i(t) + d_i m_i(t - \tau), \quad i = 1, 2, \dots, n\end{aligned}\quad (1)$$

where $m_i(t)$, $p_i(t) \in \mathbb{R}$ are concentrations of mRNA and protein of the i th node at time t , respectively, a_i and c_i are the degradation rates of the mRNA and protein, d_i is the translation rate, and $g_j(x) = (x/\beta_j)^H / [1 + (x/\beta_j)^H]$ is a monotonically increasing function with H as the Hill coefficient and β as a positive constant. The matrix $G = (G_{ij}) \in \mathbb{R}^{n \times n}$ is the coupling matrix of the GRN. l_i is defined as a basal rate.

System (1) can be written into compact matrix form

$$\begin{aligned}\frac{dm(t)}{dt} &= Em(t) + Gg(p(t - \tau)) + l, \\ \frac{dp(t)}{dt} &= Cp(t) + Dm(t - \tau),\end{aligned}\quad (2)$$

where $m(t) = [m_1(t), \dots, m_n(t)]^T$, $p(t) = [p_1(t), \dots, p_n(t)]^T$, $E = \text{diag}\{-e_1, \dots, -e_n\}$, $C = \text{diag}\{-c_1, \dots, -c_n\}$, $D = \text{diag}\{-d_1, \dots, -d_n\}$, $l = [l_1, \dots, l_n]^T$ and $g(p(t - \tau)) = [g_1(p_1(t - \tau)), \dots, g_n(p_n(t - \tau))]^T$.

Letting $[(p^*)^T, (m^*)^T]^T$ be an equilibrium of (2), the following equations are satisfied

$$\begin{aligned}0 &= Em^* + Gg(p^*) + l, \\ 0 &= Cp^* + Dm^*.\end{aligned}\quad (3)$$

Next, let us shift the equilibrium $[(p^*)^T, (m^*)^T]^T$ of system (2) to the origin. Using the transformation $\bar{m}(t) = m(t) - m^*$, $\bar{p}(t) = p(t) - p^*$, system (2) can be transformed into the following form:

$$\begin{aligned}\frac{d\bar{m}(t)}{dt} &= E\bar{m}(t) + G\bar{h}(\bar{p}(t - \tau)), \\ \frac{d\bar{p}(t)}{dt} &= C\bar{p}(t) + D\bar{m}(t - \tau),\end{aligned}\quad (4)$$

where $\bar{m}(t) = [\bar{m}_1(t), \dots, \bar{m}_n(t)]^T$, $\bar{p}(t) = [\bar{p}_1(t), \dots, \bar{p}_n(t)]^T$, and $\bar{h}(\bar{p}(t - \tau)) = [h_1(\bar{p}_1(t - \tau)), \dots, h_n(\bar{p}_n(t - \tau))]^T$ with

$$h_j(\bar{p}_j(t)) = g_j(\bar{p}_j(t) + p^*) - g_j(p^*). \quad (5)$$

Now we consider the following delayed GRN:

$$\frac{d\bar{x}(t)}{dt} = \bar{A}\bar{x}(t) + \bar{B}\bar{f}(\bar{x}(t - \tau)), \quad (6)$$

where

$$\begin{aligned}\bar{A} &= \begin{bmatrix} E & 0 \\ 0 & C \end{bmatrix}, \bar{B} = \begin{bmatrix} 0 & G \\ D & 0 \end{bmatrix}, \\ \bar{x}(t) &= \begin{bmatrix} \bar{m}(t) \\ \bar{p}(t) \end{bmatrix}, \bar{f}(\bar{x}(t - \tau)) = \begin{bmatrix} \bar{m}(t - \tau) \\ h(\bar{p}(t - \tau)) \end{bmatrix}.\end{aligned}\quad (7)$$

Actually, it's not sufficient to describe a GRN with only mRNAs and proteins. Based on the earlier discussion, a more general GRN model is proposed as follows:

$$\dot{x}(t) = Ax(t) + Bf(x(t - \tau)), \quad (8)$$

where x_1, \dots, x_n are metabolites, such as genes, proteins, activators, repressors, enzymes, factors or products of a biochemical network, and $x(\cdot) = [x_1(\cdot), \dots, x_n(\cdot)]^T \in \mathbb{R}^n$ is the metabolites state vector. Their rates of degradation are denoted by $a_i \in \mathbb{R}^+$. \dot{x}_i , the rate of change in x_i , represents concentration change of a variable due to production or degradation. $f(\cdot) = [f_1(\cdot), \dots, f_n(\cdot)]^T$ represents the regulation function on the i th metabolite, which is generally a nonlinear or linear function on the variables $[x_1(\cdot), \dots, x_n(\cdot)]$, but has a form of monotonicity for each variable. Generally speaking, A defines the degradation parameters matrix with non-diagonal plane elements zero, B defines the coupling topology, direction, and the transcriptional rate of the GRN [4].

To establish our main results, it is necessary to make the following assumption.

Assumption 1: Each function g_j in (1), $g_j(\cdot)$, $j = 1, 2, \dots, n$, satisfies the following condition:

$$l_j^- \leq \frac{g_j(x) - g_j(y)}{x - y} \leq l_j^+, \quad \forall x, y \in \mathbb{R}, x \neq y, \quad i = 1, 2, \dots, n, \quad (9)$$

where l_j^- and l_j^+ are nonnegative constants.

By (5), (7) and Assumption 1 it is not difficult to verify that

$$l_j^- \leq \frac{f_j(x) - f_j(y)}{x - y} \leq l_j^+, \quad \forall x, y \in \mathbb{R}, x \neq y, \quad i = 1, 2, \dots, n, \quad (10)$$

and it is easy to see that $f_j(0) = 0$.

To justify the network model to be considered in this paper, we will justify the inclusion of process noises, parameter uncertainty and stochastic delays in a step-by-step way in the following subsections.

A. Model with Additive Noise

Based on the Langevin approach [8], [17], the deterministic differential equations describing the dynamics of the system are modified by adding stochastic terms [9] that reflect the noise from different sources: intrinsic noise due to low numbers of molecules and extrinsic noise in cellular components that change the reaction rates for all genes [15]. We assume the noises from different sources can be

quantified and determined, and then obtain the following Langevin equation

$$\dot{x}(t) = Ax(t) + Bf(x(t - \tau)) + \sum_{j=1}^q E_j \xi_j(t). \quad (11)$$

Since the intensity of white noise can be absorbed to E_j , $\xi_j(t)$, $j = 1, \dots, q$ is additive white noise term satisfying the following statistical property

$$\begin{aligned} \mathbf{E}\{\xi_j(t)\} &= 0, \\ \mathbf{Cov}\{\xi_j(t)\xi_j(t')\} &= \delta(t - t'), \\ \mathbf{Cov}\{\xi_i(t)\xi_j(t)\} &= 0, i \neq j. \end{aligned}$$

which also implies that noises from different sources are independent.

In views of the stochastic perturbations, we arrive at the following Itô-type differential equation model:

$$dx(t) = [Ax(t) + Bf(x(t - \tau(t)))]dt + \sum_{j=1}^q E_j d\omega_j(t), \quad (12)$$

where the vector process $\omega(t) = (\omega_1(t), \dots, \omega_q(t))$ is a standard Wiener process. That is, $\omega_i(t)$, $i = 1, \dots, q$, are Brownian motions satisfying

$$\mathbf{E}\{d\omega_i(t)\} = 0, \mathbf{E}\{d\omega_i^2(t)\} = dt, \mathbf{E}\{d\omega_i(t)d\omega_j(t)\} = 0.$$

B. Model with Uncertainty

We note that acquiring parameters of the model depends on the selection of fixed point and relevant constants dependent on experiment data. As discussed earlier, stochastic events manifests that noises do exist during the process of gene expression, from the level of promoter binding to mRNA translation to protein degradation. Then, the model parameters are inevitably affected by the noises, resulting in the parameter uncertainty. We introduce uncertain matrix $\Delta A(t)$ and ΔB into (11) by allowing the parameters of A and B to vary stochastically, and then have the following Langevin equation

$$\dot{x}(t) = (A + \Delta A)x(t) + (B + \Delta B)f(x(t - \tau)) + \sum_{j=1}^q E_j \xi_j(t), \quad (13)$$

where the uncertainty matrices ΔA and ΔB are introduced to account for the noise perturbation and defined by

$$\Delta A = \sum_{j=1}^q C_j \xi_j(t), \quad \Delta B = \sum_{j=1}^q D_j \xi_j(t).$$

Then we have the following model

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bf(x(t - \tau)) \\ &+ \sum_{j=1}^q [C_j x(t) + D_j f(x(t - \tau(t))) + E_j] \xi_j(t), \end{aligned} \quad (14)$$

where the range of random uncertainty can be quantized by C_j and D_j . Of course, if some elements of A or B are free of noise disturbance, then the corresponding elements of ΔC or ΔD should be zero.

Remark 1: In the control literature, the uncertain parameter matrix $\Delta A(t)$ often refers to be *structure uncertainties*

$$\Delta A(t) = DF(t)E, \quad (15)$$

where D, E are known real constant matrices and $F(\cdot) : \mathbb{R} \rightarrow \mathbb{R}^{k \times l}$ is an unknown time-varying matrix function with Lebesgue measurable elements and such that $F^T(t)F(t) \leq I$. Studies on such uncertainties are extremely fruitful since the early work [10], and there is a rather standard LMI method to deal with such uncertainties. We like to point out that: 1) the main results of this paper can be easily extended to the model with such kind of structure uncertainties and 2) the uncertainties considered in this paper are described as stochastic processes, which are not only bounded like structure uncertainties but also more practical than structure uncertainties in modeling gene expression networks.

C. Model with Stochastic Delay

It has been recognized that the slow processes of transcription, translation and diffusion to the place of action of a protein inevitably cause time delays, which should be taken into account in the biological systems or artificial genetic networks in order to have more accurate models. Due to noise and current technological limitations, time delays may not be estimated precisely. Nevertheless, we could manage to obtain the statistical property, i.e., mean and variance values of the stochastic delays. With such information, we can model time-varying delay as a stochastic process by

$$\tau(t) = \tau_0 + \xi_\tau(t), \quad (16)$$

where τ_0 is a positive constant and $\xi_\tau(t)$ is a white noise with zero mean and σ_τ^2 variance. Then $\tau(t)$ is a stochastic process with τ_0 mean and σ_τ^2 variance, and we can then rewrite the Langevin equation as follows

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bf(x(t - \tau(t))) \\ &+ \sum_{j=1}^q [C_j x(t) + D_j f(x(t - \tau(t))) + E_j] \xi_j(t). \end{aligned} \quad (17)$$

Recalling Chebyshev's inequality, we let τ be a random variable with expected value τ_0 and finite variance σ_τ^2 . Then for any real number $\varepsilon > 0$,

$$\Pr\{|\tau - \tau_0| < \varepsilon\} \geq 1 - \frac{\sigma_\tau^2}{\varepsilon^2}. \quad (18)$$

Define

$$\tau_m = \tau_0 - \varepsilon, \tau_M = \tau_0 + \varepsilon$$

and, especially, we assume $\varepsilon = 4\sigma_\tau^2$. Then

$$\Pr\{\tau \in [\tau_0 - 4\sigma_\tau^2, \tau_0 + 4\sigma_\tau^2]\} \geq 0.9375.$$

We like to comment that the above probability is acceptable from the engineering perspective.

Remark 2: $\xi_\tau(t)$ may or may not have any relationship with intrinsic and extrinsic noise of GRN. Here, we just propose an ideal mathematical description of time-varying

delay. With such a noise term, time delays are also time-varying but not differentiable. The purpose of introducing Chebyshev's inequality is an estimation of $\tau(t)$. Given an admissible probability, the range of time delay is determined. Also, given an admissible ε , the probability when $\tau(t) \in (\tau_m, \tau_M)$ is determined. τ_m and τ_M can be treated as upper and lower bound estimation of $\tau(t)$. We notice that both τ_m and τ_M contain the information about mean and variance of $\tau(t)$. Obviously, the selection of ε might give rise to the conservatism.

D. Nominal Model

To sum up the previous discussions, we arrive at the nominal model by Itô formula

$$\begin{aligned} dx(t) &= [Ax(t) + Bf(x(t - \tau(t)))]dt \\ &\quad + \sum_{j=1}^q [C_j x(t) + D_j f(x(t - \tau(t))) + E_j] d\omega_j(t), \\ z(t) &= Fx(t), \quad x(t) = \phi(t), \quad \forall t \in [-\tau_M, 0]. \end{aligned} \quad (19)$$

$z(t)$ denotes the concentration of some genes or proteins that we are interested in. If we want to discuss the whole GRN, then we can let $F = I$.

Definition 1: The nominal system (19) with $E_j = 0$, $j = 1, \dots, q$, is said to be mean-square stable if, for any $\varepsilon > 0$, there is a $\delta(\varepsilon) > 0$ such that

$$\mathbf{E}\|x(t)\|^2 < \varepsilon, \quad t > 0,$$

when

$$\sup_{-\mu \leq s \leq 0} \mathbf{E}\|\phi(s)\|^2 < \delta(\varepsilon).$$

If, in addition,

$$\lim_{t \rightarrow \infty} \mathbf{E}\|x(t)\|^2 = 0$$

holds for any initial conditions, then the nominal system (19) with $E_j = 0$, $j = 1, \dots, q$, is said to be mean-square asymptotically stable.

Definition 2: Given a scalar $\gamma > 0$, the nominal system (19) is said to be robustly stochastically stable with disturbance attenuation γ if it is robustly stochastically stable and, under zero initial conditions, $\|z(t)\|_{E_2} < \gamma \sum_{j=1}^q \|n_j(t)\|_2$ for all nonzero $n_j(t) \in L_2[0, \infty)$, where

$$\begin{aligned} \|z(t)\|_{E_2} &= \left(\mathbf{E} \left\{ \int_0^\infty \|z(t)\|^2 dt \right\} \right)^{1/2}, \\ \|n_j(t)\|_2 &= \|E_j \xi_j(t)\|_2 = (E_j^T E_j)^{1/2}. \end{aligned}$$

Lemma 1: [24] For any vectors $x, y \in \mathbb{R}^n$, matrices $P > 0$, then

$$2x^T y \leq x^T P^{-1} x + y^T P y \quad (20)$$

Lemma 2: (Schur complement [2]) The following LMI $\begin{pmatrix} Q(x) & S(x) \\ S^T(x) & R(x) \end{pmatrix} > 0$, where $Q(x) = Q^T(x)$, $R(x) = R^T(x)$ and $S(x)$ depend affinely on x , is equivalent to $Q(x) > 0$ and $Q(x) - S^T(x)R^{-1}(x)S(x) > 0$.

III. ROBUST STABILITY ANALYSIS

In this section, we will present the robust stability criterion for the stochastic GRNs model (19).

Theorem 1: Consider the nominal stochastic delayed GRN (19). Suppose $\tau(t)$ is a stochastic process with mean τ_0 and variance σ_τ^2 , and for a given constant ε , let $\tau_m = \tau_0 - \varepsilon$, $\tau_M = \tau_0 + \varepsilon$. Then (19) is mean-square asymptotically stable with disturbance attenuation level γ , if there exist matrices $P > 0$, $Q_1 > 0$, $Q_2 > 0$, $S_i > 0, i = 1, 2, 3$, $T^- = \text{diag}\{t_1^-, \dots, t_n^-\} \geq 0$, $T^+ = \text{diag}\{t_1^+, \dots, t_n^+\} \geq 0$, X, Y, M and N satisfying

$$\begin{bmatrix} \Xi_1 + \Xi_2 & \Xi_3 \\ * & \Xi_4 \end{bmatrix} < 0, \quad (21)$$

where

$$\begin{aligned} \Xi_1 &= \Theta_1 + \Theta_2 + \Theta_2^T + \Theta_3, \\ \Xi_2 &= \Lambda_1 + \Lambda_2 + \Lambda_3, \\ \Xi_3 &= \begin{bmatrix} X & Y & M & N \end{bmatrix}, \\ \Xi_4 &= \text{diag} \left\{ -(1 + \tau_m)^{-1} S_1, -(1 + 2\varepsilon)^{-1} S_2, \right. \\ &\quad \left. -(1 + 2\varepsilon)^{-1} S_2, -(1 + \tau_M)^{-1} S_3 \right\}, \\ \Theta_1 &= W_x^T (Q_1 + Q_2) W_x - W_{Q_1}^T Q_1 W_{Q_1} - W_{Q_2}^T Q_2 W_{Q_2} \\ &\quad - 2W_f^T T^+ W_f + 2W_f^T T^- W_f, \\ \Theta_2 &= W_x^T P W_y + X W_x + Y W_y + M W_M \\ &\quad + N W_N + W_h^T T^+ L^+ W_f - W_h^T T^- L^- W_f, \\ \Theta_3 &= -\gamma^2 \sum_{j=1}^q W_{v_j}^T W_{v_j}, \\ \Lambda_1 &= W_y^T (\tau_m S_1 + 2\varepsilon S_2 + \tau_M S_3) W_y, \\ \Lambda_2 &= \sum_{j=1}^q W_{g_j}^T (P + \tau_m S_1 + 2\varepsilon S_2 + \tau_M S_3) W_{g_j}, \\ \Lambda_3 &= W_z^T W_z, \\ W_x &= \begin{bmatrix} I_n & 0_{n, 4n+q} \end{bmatrix}, \\ W_y &= \begin{bmatrix} A & 0_{n, 3n} & B & 0_{n, q} \end{bmatrix}, \\ W_z &= \begin{bmatrix} F & 0_{n, 4n+q} \end{bmatrix}, \\ W_f &= \begin{bmatrix} 0_{n, 4n} & I_n & 0_{n, q} \end{bmatrix}, \\ W_{g_j} &= \begin{bmatrix} C_j & 0_{n, 3n} & D_j & 0_{n, j-1} & E_j & 0_{n, q-j} \end{bmatrix}, \\ W_h &= \begin{bmatrix} 0_{n, 2n} & I_n & 0_{n, 2n+q} \end{bmatrix}, \\ W_{v_j} &= \begin{bmatrix} 0_{n, 5n} & 0_{n, j-1} & E_j & 0_{n, q-j} \end{bmatrix}, \\ W_{Q_1} &= \begin{bmatrix} 0_n & I_n & 0_{n, 3n+q} \end{bmatrix}, \\ W_{Q_2} &= \begin{bmatrix} 0_{n, 3n} & I_n & 0_{n, n+q} \end{bmatrix}, \\ W_X &= \begin{bmatrix} I_n & -I_n & 0_{n, 3n+q} \end{bmatrix}, \\ W_Y &= \begin{bmatrix} 0_n & I_n & -I_n & 0_{n, 2n+q} \end{bmatrix}, \\ W_M &= \begin{bmatrix} 0_{n, 2n} & I_n & -I_n & 0_{n, n+q} \end{bmatrix}, \\ W_N &= \begin{bmatrix} I_n & 0_{2n} & -I_n & 0_{n, n+q} \end{bmatrix}. \end{aligned} \quad (22)$$

Proof. For convenience, set

$$\begin{aligned} y(t) &= Ax(t) + Bf(x(t - \tau(t))), \\ g_j(t) &= C_j x(t) + D_j f(x(t - \tau(t))) + E_j. \end{aligned}$$

Then, the first equation in (19) becomes

$$dx(t) = y(t)dt + \sum_{j=1}^q g_j(t)d\omega_j(t). \quad (23)$$

Define a Lyapunov-Krasovskii functional candidate for system (19):

$$V(x_t, t) = \sum_{k=1}^4 V_k(x_t, t),$$

where

$$\begin{aligned} V_1(x_t, t) &= x^T(t)Px(t), \\ V_2(x_t, t) &= \int_{t-\tau_m}^t x^T(\alpha)Q_1x(\alpha)d\alpha \\ &\quad + \int_{t-\tau_M}^t x^T(\alpha)Q_2x(\alpha)d\alpha, \\ V_3(x_t, t) &= \int_{t-\tau_m}^0 \int_{\beta}^0 y^T(\alpha)S_1y(\alpha)d\alpha d\beta \\ &\quad + \int_{t-\tau_m}^0 \int_{\beta}^0 y^T(\alpha)S_2y(\alpha)d\alpha d\beta \\ &\quad + \int_{t-\tau_M}^0 \int_{\beta}^0 y^T(\alpha)S_3y(\alpha)d\alpha d\beta, \\ V_4(x_t, t) &= \sum_{j=1}^q \left[\int_{t-\tau_m}^0 \int_{\beta}^0 g_j^T(\alpha)S_1g_j(\alpha)d\alpha d\beta \right. \\ &\quad + \int_{t-\tau_m}^0 \int_{\beta}^0 g_j^T(\alpha)S_2g_j(\alpha)d\alpha d\beta \\ &\quad \left. + \int_{t-\tau_M}^0 \int_{\beta}^0 g_j^T(\alpha)S_3g_j(\alpha)d\alpha d\beta \right]. \quad (24) \end{aligned}$$

Here $P, Q_1, Q_2, S_i, i = 1, 2, 3$, are positive definite matrices with appropriate dimensions. Employing Itô's formula, we obtain the stochastic differential as

$$dV(t) = \mathcal{L}V(t)dt + 2x^T(t)P \sum_{j=1}^q g_j(t)d\omega_j(t), \quad (25)$$

where

$$\begin{aligned} \mathcal{L}V_1(t) &= 2x^T(t)Py(t) + \sum_{j=1}^q g_j^T(t)Pg_j(t), \\ \mathcal{L}V_2(t) &= x^T(t)(Q_1 + Q_2)x(t) \\ &\quad - x^T(t - \tau_m)Q_1x(t - \tau_m) \\ &\quad - x^T(t - \tau_M)Q_2x(t - \tau_M), \\ \mathcal{L}V_3(t) &= y^T(t)(\tau_m S_1 + 2\epsilon S_2 + \tau_M S_3)y(t) \\ &\quad - \int_{t-\tau_m}^t y^T(\alpha)S_1y(\alpha)d\alpha \\ &\quad - \int_{t-\tau_M}^{t-\tau(t)} y^T(\alpha)S_2y(\alpha)d\alpha \\ &\quad - \int_{t-\tau(t)}^{t-\tau_m} y^T(\alpha)S_2y(\alpha)d\alpha \\ &\quad - \int_{t-\tau_M}^t y^T(\alpha)S_3y(\alpha)d\alpha \end{aligned}$$

$$\begin{aligned} \mathcal{L}V_4(t) &= \sum_{j=1}^q g_j^T(t)(\tau_m S_1 + 2\epsilon S_2 + \tau_M S_3)g_j(t) \\ &\quad - \sum_{k=1}^4 U_k, \end{aligned} \quad (26)$$

with

$$\begin{aligned} U_1 &= \sum_{j=1}^q \int_{t-\tau_m}^t g_j^T(\alpha)S_1g_j(\alpha)d\alpha, \\ U_2 &= \sum_{j=1}^q \int_{t-\tau(t)}^{t-\tau_m} g_j^T(\alpha)S_2g_j(\alpha)d\alpha, \\ U_3 &= \sum_{j=1}^q \int_{t-\tau_M}^{t-\tau(t)} g_j^T(\alpha)S_2g_j(\alpha)d\alpha, \\ U_4 &= \sum_{j=1}^q \int_{t-\tau_M}^t g_j^T(\alpha)S_3g_j(\alpha)d\alpha. \end{aligned} \quad (27)$$

From (23), for any appropriately dimensioned matrix X, Y, M and N , we have

$$\begin{aligned} 0 &= 2\zeta^T(t)X[x(t) - x(t - \tau_m) \\ &\quad - \int_{t-\tau_m}^t y(\alpha)d\alpha - \sum_{j=1}^q \int_{t-\tau_m}^t g_j(\alpha)d\omega_j(\alpha)], \\ 0 &= 2\zeta^T(t)Y[x(t - \tau_m) - x(t - \tau(t)) \\ &\quad - \int_{t-\tau(t)}^{t-\tau_m} y(\alpha)d\alpha - \sum_{j=1}^q \int_{t-\tau(t)}^{t-\tau_m} g_j(\alpha)d\omega_j(\alpha)], \\ 0 &= 2\zeta^T(t)M[x(t - \tau(t)) - x(t - \tau_M) \\ &\quad - \int_{t-\tau_M}^{t-\tau(t)} y(\alpha)d\alpha - \sum_{j=1}^q \int_{t-\tau_M}^{t-\tau(t)} g_j(\alpha)d\omega_j(\alpha)], \\ 0 &= 2\zeta^T(t)N[x(t) - x(t - \tau_M) \\ &\quad - \int_{t-\tau_M}^t y(\alpha)d\alpha - \sum_{j=1}^q \int_{t-\tau_M}^t g_j(\alpha)d\omega_j(\alpha)], \end{aligned} \quad (28)$$

where the augmented vector is

$$\begin{aligned} \zeta^T(t) &= [x^T(t) \quad x^T(t - \tau_m) \quad x^T(t - \tau(t)) \\ &\quad x^T(t - \tau_M) \quad f^T(x(t - \tau(t))) \quad e^T], \\ e &= [1 \quad \dots \quad 1]^T \in \mathbb{R}^q. \end{aligned}$$

From Lemma 1 for any appropriately dimensioned matrices $S_i > 0, i = 1, 2, 3$, then we have

$$\begin{aligned} -2\zeta^T(t)X\Sigma_1 &\leq \zeta^T(t)XS_1^{-1}X^T\zeta(t) + \Sigma_1^T S_1 \Sigma_1, \\ -2\zeta^T(t)Y\Sigma_2 &\leq \zeta^T(t)YS_2^{-1}Y^T\zeta(t) + \Sigma_2^T S_2 \Sigma_2, \\ -2\zeta^T(t)M\Sigma_3 &\leq \zeta^T(t)MS_2^{-1}M^T\zeta(t) + \Sigma_3^T S_2 \Sigma_3, \\ -2\zeta^T(t)N\Sigma_4 &\leq \zeta^T(t)NS_3^{-1}N^T\zeta(t) + \Sigma_4^T S_3 \Sigma_4, \end{aligned} \quad (29)$$

where

$$\begin{aligned}
\Sigma_1 &= \sum_{j=1}^q \int_{t-\tau_m}^t g_j(\alpha) d\omega_j(\alpha), \\
\Sigma_2 &= \sum_{j=1}^q \int_{t-\tau(t)}^{t-\tau_m} g_j(\alpha) d\omega_j(\alpha), \\
\Sigma_3 &= \sum_{j=1}^q \int_{t-\tau_M}^{t-\tau(t)} g_j(\alpha) d\omega_j(\alpha), \\
\Sigma_4 &= \sum_{j=1}^q \int_{t-\tau_M}^t g_j(\alpha) d\omega_j(\alpha). \quad (30)
\end{aligned}$$

By (10), for any scalar $t_j^+ \geq 0$, it is clear that

$$0 \leq 2 \sum_{j=1}^n t_j^+ f_j(x_j(t-\tau(t))) \left[l_j^+ x_j(t-\tau(t)) - f_j(x_j(t-\tau(t))) \right], \quad (31)$$

or equivalently

$$0 \leq 2[f(x(t-\tau(t)))T^+L^+x(t-\tau(t)) - f(x(t-\tau(t)))T^+f(x(t-\tau(t)))]. \quad (32)$$

For any scalar $t_j^- \geq 0$, it is clear that

$$0 \leq 2 \sum_{j=1}^n t_j^- f_j(x_j(t-\tau(t))) \left[f_j(x_j(t-\tau(t))) - l_j^- x_j(t-\tau(t)) \right], \quad (33)$$

or equivalently

$$0 \leq 2[f(x(t-\tau(t)))T^-f(x(t-\tau(t))) - f(x(t-\tau(t)))T^-L^-x(t-\tau(t))]. \quad (34)$$

Therefore, from (26)–(34) we have

$$\begin{aligned}
\mathcal{LV}(t) &\leq F + (\Sigma_1^T S_1 \Sigma_1 + \Sigma_2^T S_2 \Sigma_2 + \Sigma_3^T S_2 \Sigma_3 \\
&\quad + \Sigma_4^T S_3 \Sigma_4) - \sum_{k=1}^4 U_k - \sum_{k=1}^4 \Omega_k \quad (35)
\end{aligned}$$

where

$$\begin{aligned}
F &\triangleq 2x^T(t)Py(t) + \sum_{j=1}^q g_j^T(t)Pg_j(t) \\
&\quad + x^T(t)(Q_1 + Q_2)x(t) - x^T(t-\tau_m)Q_1 \\
&\quad \times x(t-\tau_m) + x^T(t-\tau_m)Q_2x(t-\tau_m) \\
&\quad + y^T(t)(\tau_m S_1 + 2\epsilon S_2 + \tau_M S_3)y(t) \\
&\quad + \sum_{j=1}^q g_j^T(t)(\tau_m S_1 + 2\epsilon S_2 + \tau_M S_3)g_j(t) \\
&\quad + 2\zeta^T(t)X(x(t) - x(t-\tau_m)) \\
&\quad + 2\zeta^T(t)Y(x(t-\tau_m) - x(t-\tau(t))) \\
&\quad + 2\zeta^T(t)M(x(t-\tau(t)) - x(t-\tau_M)) \\
&\quad + 2\zeta^T(t)N(x(t) - x(t-\tau_M)) \\
&\quad + \zeta^T(t)X(1 + \tau_m)S_1^{-1}X^T\zeta(t) \\
&\quad + \zeta^T(t)Y(1 + 2\epsilon)S_2^{-1}Y^T\zeta(t) \\
&\quad + \zeta^T(t)M(1 + 2\epsilon)S_2^{-1}M^T\zeta(t) \\
&\quad + \zeta^T(t)N(1 + \tau_M)S_3^{-1}N^T\zeta(t), \\
&\quad + [2f(x(t-\tau(t)))T^+L^+x(t-h_i(t)) \\
&\quad - 2f(x(t-\tau(t)))T^+f(x(t-\tau(t)))] \\
&\quad + [2f(x(t-\tau(t)))T^-f(x(t-\tau(t)))] \\
&\quad - 2f(x(t-\tau(t)))T^-L^-x(t-\tau(t))] \\
&= \zeta^T(t) [\Xi_0 + \Theta_1 + \Theta_2 + \Theta_2^T \\
&\quad + \Theta_3 + \Lambda_1 + \Lambda_2] \zeta(t), \\
\Xi_0 &= X(1 + \tau_m)S_1^{-1}X^T + Y(1 + 2\epsilon)S_2^{-1}Y^T \\
&\quad + M(1 + 2\epsilon)S_2^{-1}M^T + N(1 + \tau_M)S_3^{-1}N^T, \quad (36)
\end{aligned}$$

where $\Theta_1, \Theta_2, \Theta_3$ are defined in (22), and

$$\begin{aligned}
\Omega_1 &= - \int_{t-\tau_m}^t [\zeta^T(t)X + y^T(\alpha)S_1] S_1^{-1} \\
&\quad \times [X^T\zeta(t) + S_1y(\alpha)] d\alpha, \\
\Omega_2 &= - \int_{t-\tau(t)}^{t-\tau_m} [\zeta^T(t)Y + y^T(\alpha)S_2] S_2^{-1} \\
&\quad \times [Y^T\zeta(t) + S_2y(\alpha)] d\alpha, \\
\Omega_3 &= - \int_{t-\tau_M}^{t-\tau(t)} [\zeta^T(t)M + y^T(\alpha)S_2] S_2^{-1} \\
&\quad \times [M^T\zeta(t) + S_2y(\alpha)] d\alpha, \\
\Omega_4 &= - \int_{t-\tau_M}^t [\zeta^T(t)N + y^T(\alpha)S_3] S_3^{-1} \\
&\quad \times [N^T\zeta(t) + S_3y(\alpha)] d\alpha. \quad (37)
\end{aligned}$$

We also have

$$\begin{aligned}
\mathbf{E}\{\Sigma_1^T S_1 \Sigma_1\} &= \mathbf{E}\{U_1\}, \\
\mathbf{E}\{\Sigma_2^T S_2 \Sigma_2\} &= \mathbf{E}\{U_2\}, \\
\mathbf{E}\{\Sigma_3^T S_2 \Sigma_3\} &= \mathbf{E}\{U_3\}, \\
\mathbf{E}\{\Sigma_4^T S_3 \Sigma_4\} &= \mathbf{E}\{U_4\}, \quad (38)
\end{aligned}$$

it follows that

$$\begin{aligned} & \mathbf{E}\{LV(t)\} \\ & \leq \mathbf{E}\{\zeta^T(t) [\Xi_0 + \Theta_1 + \Theta_2 + \Theta_2^T + \Lambda_1 + \Lambda_2] \zeta(t)\}. \end{aligned} \quad (39)$$

Now we are in a position to show that GRN (19) satisfies $\|z(t)\|_{E_2} < \gamma \sum_{j=1}^q \|n_j(t)\|_2$

$$\|z(t)\|_{E_2} < \gamma \sum_{j=1}^q \|n_j(t)\|_2 \quad (40)$$

for all nonzero $n_j(t) \in L_2[0, \infty)$, $j = 1, \dots, q$. Under zero initial condition, we have $\mathbf{E}\{V(0)\} = 0$ and $\mathbf{E}\{V(t)\} \geq 0$. Integrating both sides of (25) from 0 to $t > 0$, and then taking expectation, we have

$$\mathbf{E}\{V(t)\} = \mathbf{E}\left\{\int_0^t \mathcal{L}V(s) ds\right\}. \quad (41)$$

Define the following performance index for a prescribed $\gamma > 0$

$$J(t) = \mathbf{E}\left\{\int_0^t [z^T(s)z(s) - \gamma^2 \sum_{j=1}^q E_j^T E_j] ds\right\}. \quad (42)$$

From (39), (41) and (42), it is easy to show that

$$\begin{aligned} J(t) &= \mathbf{E}\left\{\int_0^t [z^T(s)z(s) - \gamma^2 \sum_{j=1}^q E_j^T E_j + \mathcal{L}V(s)] ds\right\} \\ &\quad - \mathbf{E}\{V(t)\} \\ &\leq \mathbf{E}\left\{\int_0^t [z^T(s)z(s) - \gamma^2 \sum_{j=1}^q E_j^T E_j + \mathcal{L}V(s)] ds\right\} \\ &\leq \mathbf{E}\left\{\int_0^t \zeta^T(s) [\Xi_0 + \Theta_1 + \Theta_2 + \Theta_2^T + \Theta_3 \right. \\ &\quad \left. + \Lambda_1 + \Lambda_2 + \Lambda_3] \zeta(s) ds\right\} \\ &\leq \mathbf{E}\left\{\int_0^t \zeta^T(s) [\Xi_0 + \Xi_1 + \Xi_2] \zeta(s) ds\right\}. \end{aligned} \quad (43)$$

By Schur complement, (21) is equivalent to (44)

$$\Xi_0 + \Xi_1 + \Xi_2 < 0. \quad (44)$$

Therefore, we have

$$J(t) < 0, \quad \forall t > 0. \quad (45)$$

Then, (40) follows immediately from (42) and (45) and the proof is completed. \square

IV. ILLUSTRATIVE EXAMPLE

In this section, we present an example to show the effectiveness and correctness of our theoretical results.

Consider the following GRN with four sources of noise in Fig. 1:

$$\begin{aligned} dx(t) &= [Ax(t) + Bf(x(t - \tau(t)))] dt \\ &\quad + \sum_{j=1}^q [C_j x(t) + D_j f(x(t - \tau(t))) + E_j] d\omega_j(t), \\ z(t) &= Fx(t). \end{aligned} \quad (46)$$

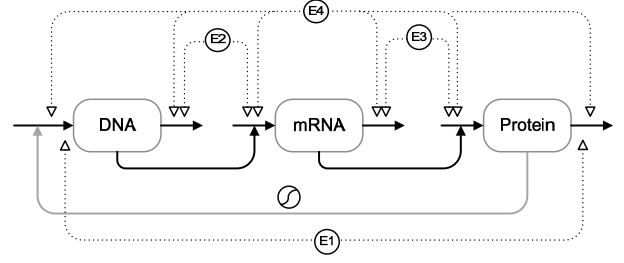


Fig. 1. A GRN with four sources of noise

where $x(t) = [d(t) \ m(t) \ p(t)]^T$, $f(x(t - \tau(t))) = [d(t - \tau(t)) \ m(t - \tau(t)) \ g(p(t - \tau(t)))]^T$. $d(t)$, $m(t)$ and $p(t)$ represent the concentration of DNA, mRNA and protein respectively. The regulation from protein to DNA can be described by $g(x) = x^2 / (1 + x^2)$. It is easy to know $\dot{g}(x) \in [0, 0.65]$. Then we take $L^- = \text{diag}\{1, 1, 0\}$ and $L^+ = \text{diag}\{1, 1, 0.65\}$. For simplicity, we assume intensity of all noises to be unit. Then we get

$$E_1 = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, E_2 = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}, E_3 = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}, E_4 = \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}.$$

The stochastic time delay $\tau(t)$ has expected value $\tau_0 = 0.3$ and variance $\sigma_\tau^2 = 0.05^2$. We select $\varepsilon = 4\sigma_\tau$, the probability $\tau(t) \in (0.1, 0.5)$ is at least 0.9375. And the system matrices are given as follows:

$$\begin{aligned} A &= \text{diag}\{-0.0985, -5, -3\}, \\ B &= \begin{bmatrix} 0 & 0 & -0.3962 \\ 0.1971 & 0 & 0 \\ 0 & 2 & 0 \end{bmatrix}, \\ C_1 &= \text{diag}\{-0.0414, 0, 0\}, \\ C_2 &= \text{diag}\{0, -1.4000, 0\}, \\ C_3 &= \text{diag}\{0, 0, -1.0500\}, \\ C_4 &= \text{diag}\{-0.0177, -0.6000, -0.4500\}, \end{aligned}$$

$$\begin{aligned} D_1 &= \begin{bmatrix} 0 & 0 & -0.1664 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \\ D_2 &= \begin{bmatrix} 0 & 0 & 0 \\ 0.0690 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \\ D_3 &= \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0.7000 & 0 \end{bmatrix}, \\ D_4 &= \begin{bmatrix} 0 & 0 & -0.0713 \\ 0.0296 & 0 & 0 \\ 0 & 0.3000 & 0 \end{bmatrix}. \end{aligned}$$

We let $F = [0, 0, 1]$. It means that we are interested in the concentration of proteins.

By solving the condition in Theorem 1 using the LMI toolbox in Matlab, we can obtain a feasible solution for $\gamma \geq 0.9$. When the minimum allowed $\gamma = 0.9$, we get the

following obtained matrix variables (for space consideration, here we only list the matrix variables P , Q_1 and Q_2):

$$P = \begin{bmatrix} 0.1519 & -0.0124 & -0.0090 \\ -0.0124 & 0.0179 & 0.0435 \\ -0.0090 & 0.0435 & 0.3511 \end{bmatrix},$$

$$Q_1 = \begin{bmatrix} 5.7535 & -8.5077 & -4.5213 \\ -8.5077 & 22.6188 & 6.5873 \\ -4.5213 & 6.5873 & 17.0481 \end{bmatrix},$$

$$Q_2 = \begin{bmatrix} 9.6391 & -14.8919 & -6.3102 \\ -14.8919 & 40.8181 & 10.0771 \\ -6.3102 & 10.0771 & 17.0974 \end{bmatrix}.$$

The simulation result of the trajectories of $p(t)$ is shown in Fig. 2.

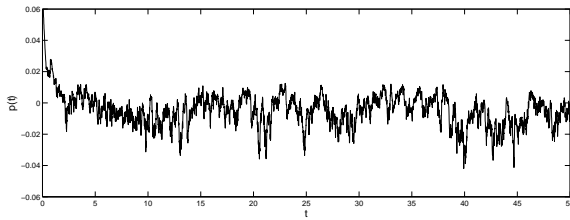


Fig. 2. Trajectories of $p(t)$ in GRN (46)

V. CONCLUSION

This paper has presented robust stability conditions for GRN with stochastic time delay. Intrinsic and extrinsic noises from different sources are considered in modeling GRN. Noises are also utilized to characterize the GRN model uncertainties. These conditions are formulated in terms of linear matrix inequalities, which can be readily solved by using standard numerical software. By utilizing some advanced techniques, both the expected value and variance of stochastic delays are brought into the final robust stability conditions. A GRN example has illustrated the applicability and usefulness of the developed theoretical results.

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